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BASIC NEUROSCIENCES, GENETICS AND IMMUNOLOGY - REVIEW ARTICLE

Circadian rhythms in obsessive–compulsive disorder

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Abstract The etiopathology and neurobiology of obsessive–compulsive disorder (OCD) are not fully understood. As for altered circadian rhythms associated with OCD, hormonal dysregulation and a delayed sleep phase have come into the focus of research. The novel antidepressant agomelatine is able to resynchronize circadian rhythms and the augmentative administration of this compound has been shown to be of benefit in some OCD patients who are refractory to common forms of pharmacotherapy. Adjunctive chronotherapy might also enhance the outcome in treatment-refractory OCD. The present review summarises the findings regarding circadian abnormalities in OCD.

Keywords Obsessive–compulsive disorder (OCD) · Circadian rhythm · Hormone dysregulation · Delayed sleep phase · Agomelatine · Chronotherapy

Introduction

Obsessive–compulsive disorder (OCD) is a common chronic neuropsychiatric disorder which results in marked distress and impairment of social and occupational functioning. OCD is characterized by clinically significant recurrent, intrusive and disturbing thoughts (obsessions) and/or repetitive stereotypic behaviors (compulsions) which are usually associated with anxiety or dread. The disorder can be inherited (for review see Pauls 2010; Walitza et al. 2010) or acquired. Approximately 2 to 3 % of the population are affected by OCD and an early age of symptom onset has been observed in many patients (Nestadt et al. 2000; Flament et al. 1988; Valleni-Basile et al. 1994). Obsessive/compulsive symptoms have been shown to increase at times of stress (Findley et al. 2003) and stressful events may precede the onset of OCD (e.g., Toro et al. 1992).

There is no established pathology for OCD and putative pathophysiological alterations have been inferred from abnormalities as observed using structural and functional neuroimaging. A review of the neurobiology of OCD is given by Grados and Wilcox (2007). A possible role of abnormal circadian rhythms in OCD is mainly based on three lines of evidence, i.e. (1) hormonal dysregulation in subjects with OCD, (2) a delayed sleep phase in some individuals with OCD and (3) effective augmentation treatment with agomelatine in patients who are refractory to commonly used forms of OCD pharmacotherapy. Agomelatine has been shown to be able to resynchronize circadian rhythms in patients with mental disorders.

Hormonal abnormalities in OCD

The interest in possible alterations of circadian rhythms in psychiatric disorders has put hormonal dysregulation into the focus of scientific investigations, since many hormones are released according to circadian patterns. In a recent review, Kalsbeek et al. (2012) have described the current view on the control by the suprachiasmatic nucleus of the daily rhythm in the activity of the hypothalamic–pituitary–adrenal (HPA) axis.

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Individuals with OCD have been reported to show alterations in hormone levels, including the concentrations of cortisol (Catapano et al. 1992; Monteleone et al. 1994), corticotrophin releasing hormone (CRH) (Altemus et al. 1992), dehydroepiandrosterone (DHEA) and its sulfated metabolite DHEA-S (Bigos et al. 2009), adrenocorticotrophic hormone (ACTH) (Bailly et al. 1994), growth hormone (Kluge et al. 2007a, b), vasopressin (Altemus et al. 1992), oxytocin (Leckman et al. 1994) and melatonin (Catapano et al. 1992; Monteleone et al. 1994).

The findings regarding the functioning of the HPA axis are inconsistent. Elevated CRH concentrations in the cerebrospinal fluid of patients with OCD (Altemus et al. 1992) suggest an increase in HPA axis activity. However, other studies failed to find this increase and similar CRH levels were observed in OCD patients and healthy control subjects (Chappell et al. 1996). A hyperactivity of the HPA axis is also indicated by the finding that a lack of inhibition of cortisol secretion after a dexamethasone suppression test can be found in some patients with OCD (Cottraux et al. 1984; Catapano et al. 1990). These observations could, however, not be confirmed by other authors (Coryell et al. 1989; Jenike et al. 1987; Lieberman et al. 1985; Lucey et al. 1992; Vallejo et al. 1988). Further information concerning HPA axis activity can be derived from secretion profiles of the stress hormones ACTH and cortisol. In comparison with control subjects, circadian cortisol secretion profiles were reported to be preserved but elevated in OCD patients (Catapano et al. 1992; Monteleone et al. 1994). Nocturnal plasma cortisol and ACTH levels were shown to be significantly increased in individuals with OCD compared to healthy controls, while the secretion patterns over time were similar in both groups (Kluge et al. 2007a, b). These findings are in accordance with earlier results indicating a hyperactive HPA axis (e.g., Altemus et al. 1992; Cottraux et al. 1984). They do not corroborate, however, the hypothesis of a decrease in pituitary sensitivity due to elevated CRH levels (Bailly et al. 1994), since ACTH was not reduced in patients with OCD.

Hyperactivity of the HPA axis, commonly observed in adult OCD patients, has also been shown to be present in children and adolescents with OCD. In comparison to a control group of school children, young individuals with OCD displayed higher early-morning basal cortisol levels with no difference between the groups in the late-morning and evening assessments (Gustafsson et al. 2008). The cortisol levels in children and adolescents with OCD diminished in response to a psychological stressor (i.e., exposure therapy), compared to a positive response in the control group (Gustafsson et al. 2008). The non-response in young OCD patients may be another example of HPA dysregulation.

Patients with OCD have been shown to suffer more severely from stress related to daily life than healthy individuals (Coles et al. 2005; Findley et al. 2003; Tarumi and Tashiiro 2004). Both physical and psychological stress can activate the HPA axis (de Kloet et al. 2005). Since patients with OCD perceive their obsessive thoughts as beyond their control, this lack of control may be a stressor leading to a chronically hyperactive HPA axis. As to the psychobiology of OCD, the increase in the activity of the HPA axis may be regarded as a result of stress, i.e. HPA alterations may be a consequence of non-specific anxiety and therefore a state rather than a trait feature of OCD. However, the resistance of the HPA axis to therapy (Millet et al. 1999; Khanna et al. 2001) points in another direction. A hyperactive HPA axis might play a role in the pathophysiology of OCD. For example, neurobiological models of OCD (Rosenberg and Keshavan 1998) posit an important role of a dysfunctional anterior cingulate gyrus (ACG) which has been suggested to be part of an overactive action-monitoring system and to be involved in the pathophysiology of OCD (Ursu et al. 2003). Structural and functional alterations of the ACG in patients with OCD (Rauch et al. 1994; Rosenberg and Keshavan 1998; Szeszko et al. 2004, 2005; Ursu et al. 2003; Viard et al. 2005) and observations suggesting a critical role of the ACG in the regulation of the HPA axis (Diorio et al. 1993; Herman et al. 2005; MacLullich et al. 2006) underline the possibility of a two-way interaction between ACG and HPA axis. For a more detailed summary of possible links between HPA axis and OCD, see Kluge et al. (2007a, b).

In OCD subjects, nocturnal growth hormone (GH) secretion has been shown to be altered, i.e. the release of sleep onset-related GH was blunted (Kluge et al. 2007a). This finding appears to be compatible with central neurotransmitter alterations assumed in OCD, indicating an influence at hypothalamic or higher levels. In a single individual with OCD, the circadian patterns of DHEA and cortisol have been reported to be markedly different from control subjects, with DHEA and DHEA-S levels being substantially higher in the OCD subject (Bigos et al. 2009). This preliminary finding requires the assessment of larger patient samples. A dysregulation of DHEA and DHEA-S has also been reported in other mood and anxiety disorders (Eser et al. 2006; Le Melledo and Baker 2002, 2004). For example, subjects with major depression show increased diurnal plasma DHEA (Heuser et al. 1998) and both DHEA and DHEA-S have been found to decrease with the remission of depression (Fabian et al. 2001). The relative amounts of DHEA and/or DHEA-S appear to be maintained between blood and brain (Bernardi et al. 2005; Guazzo et al. 1996). Increased DHEA/DHEA-S blood levels should therefore indicate elevated DHEA/DHEA-S concentrations in the brain. DHEA and DHEA-S are

modulators of $GABA_A$ (Le Melledo and Baker 2004; Majewska 1992; Majewska et al. 1990; Reddy and Kulkarni 1997) and *N*-methyl-D-aspartate (NMDA) receptors (Compagnone and Mellon 2000; Rupprecht 1997) and are also involved in NMDA-induced norepinephrine release (Monnet et al. 1995). Since altered central norepinephrine levels appear to be associated with other anxiety disorders (Sullivan et al. 1999), DHEA dysregulation may play a role in OCD-related anxiety.

Alterations in the circadian secretion of melatonin have been reported in OCD. In medication-free individuals with OCD, the night-time peak of melatonin concentrations was shown to be markedly reduced in comparison with control subjects and occurred with a delay of 2 h (Monteleone et al. 1994). These abnormalities were more pronounced in patients with more severe OCD symptoms as assessed with the Yale-Brown Obsessive Compulsive Scale (Y-BOCS, Goodman et al. 1989). A delay in peak melatonin would usually result in a phase delay of sleep.

Delayed sleep phase syndrome in OCD

Mental disorders are frequently accompanied by sleep disturbance. The few studies examining possible sleep disturbance in OCD have reported contradictory findings, including an undisturbed sleep pattern observed in some studies (Hohagen et al. 1994) and sleep disruption found in others (Insel et al. 1982; Rapoport et al. 1981). Investigations in both adults (Insel et al. 1982) and adolescents (Rapoport et al. 1981) with OCD found a reduced total sleep duration, a decrease in stage 2 sleep and a shortened rapid eye movement (REM) latency. Stage 4 sleep and slow-wave sleep were reported to be increased (Rapoport et al. 1981) or decreased (Insel et al. 1982) in OCD. The OCD patients in these studies (Hohagen et al. 1994; Insel et al. 1982; Rapoport et al. 1981) concomitantly suffered from depression. In a recent study, the sleep variables did not differ between patients with OCD without comorbid major depression and healthy matched control subjects (Kluge et al. 2007a). Out of ten patients, three subjects, who appeared to be more severely affected by OCD than the others, exhibited sleep onset REM periods (Kluge et al. 2007a). In comparison with control subjects, Bobdey et al. (2001) observed no significantly different sleep pattern in OCD patients without depression. A small subgroup of these patients, however, went to bed and arose much later than normal. This delayed sleep phase syndrome (DSPS) results in daytime sleepiness and a considerable disruption of social and occupational functioning (Weitzman et al. 1981). The prevalence of DSPS in the general adult population is estimated at 0.17–0.72 % (Schrader et al. 1993). Elevated rates of 7.3 % in adolescents (American Psychiatric Association 1994) and up to 10 % in children (Smits et al. 2001) have been reported. Differences between the sexes were not found (Dagan and Eisenstein 1999). Almost 50 % of adult individuals with DSPS have been reported to show psychiatric symptoms (Weitzman et al. 1981) with depressive disorder being the most common psychiatric concomitant (Zammit 1997).

A retrospective study reported a possible association between OCD and DSPS (Mukhopadhyay et al. 2004). A more recent retrospective study identified 17.6 % of 187 cases with severe, enduring OCD who were also affected by DSPS (Mukhopadhyay et al. 2008). In a prospective study, individuals with therapy-refractory OCD showed an increased rate of delayed sleep phase, i.e. 42 % out of a total of 31 patients with severe resistant OCD suffered from DSPS (Turner et al. 2007). No other sleep parameter apart from the timing of sleep was observed to be significantly different. Patients with DSPS were significantly more likely to be male, were younger and showed more severe OCD than those with a normal sleep phase (Mukhopadhyay et al. 2008; Turner et al. 2007). The delayed sleep phase in the patients reported by Turner et al. (2007) was not due to patients performing bedtime rituals or taking longer to fall asleep. The DSPS in OCD patients was associated with an increase in disablement in occupational and social functioning (Turner et al. 2007). It is, however, unclear whether this reflected the shifted sleep pattern or the more severe OCD.

Circadian rhythms are entrained by temporal cues and environmental zeitgebers such as the light–dark cycle. Various stressors or behavioral patterns may cause disruptions in social routines and as a consequence in biological rhythms according to the social zeitgeber theory (Grandin et al. 2006). OCD patients presenting with complex ritualistic behavior at home may be insufficiently exposed to light in the morning. In addition, lack of activity and social withdrawal may hinder the daily resetting of the biological clock. These behavioral patterns may eventually result in a phase delay of sleep. Weitzman et al. (1981) argue, however, that DSPS is the cause and not the result of psychological symptoms in mental disorders, since the treatment of the sleep disorder can lead to a marked improvement in psychological functioning. Other authors support the idea that DSPS precedes and may therefore contribute to the development of mental disorder (Dagan et al. 1996, 1998). With regard to personality disorders, Dagan et al. (1996, 1998) have suggested that a mismatch between a person's biological clock and the environment may cause social and emotional difficulties. As for individuals with OCD, however, it needs to be noted that delayed sleep phase developed after the onset of OCD in the patients reported by Turner et al. (2007). In addition, OCD patients who responded satisfactorily to fluoxetine treatment showed no difference in biological parameters,

such as temperature and plasma levels of cortisol and melatonin, as assessed before and after treatment (Millet et al. 1999; Monteleone et al. 1995).

A recent report has described a patient with severe OCD who had failed prior trials of pharmacotherapy and psychotherapy and whose symptoms were associated with delayed bedtimes and delays in the time she initiated her night-time compulsions (Coles and Sharkey 2011). Later, at the time of initiation, her compulsions were associated with more time spent performing her compulsions. Cognitive-behavioral techniques commonly used for OCD with adjunctive chronotherapy (i.e., advancement of sleep-wake schedule) were associated with substantial improvement of her compulsive behavior at night. Further studies are needed in order to establish whether chronotherapy may enhance the outcome in treatment-refractory OCD, particularly in individuals with night-time compulsions.

Augmentation with agomelatine for the treatment of OCD

The pharmacotherapy with selective serotonin reuptake inhibitors (SRIs) is well established for the treatment of OCD. Forty to 60 % of patients with OCD, however, do not respond satisfactorily to SRIs (Bloch et al. 2006; da Rocha and Correa 2007; Pallanti et al. 2002). The low-dose augmentative administration of dopamine antagonists such as risperidone has been shown to be effective in some patients who are refractory to SRIs (Bloch et al. 2006).

Recent reports have presented evidence that the augmentation with agomelatine may also be helpful in OCD patients who are resistant to common forms of pharmacotherapy and do not respond to augmentation with other compounds. Agomelatine is a novel antidepressant which is a melatonergic agonist at melatonin 1 (MT1) and MT2 receptors and acts as a selective serotonin antagonist at the 5-hydroxytryptamine (HT)2C receptor, while it does not appear to affect monoamine uptake (de Bodinat et al. 2010). The blockade of 5-HT2C receptors is of interest since these receptors are involved in mood control and stress response. Serotonin has been shown to be synthesized according to a circadian pattern (e.g. Sanchez et al. 2008) and the suprachiasmatic nucleus, the dominant force for the circadian rhythms controlling sleep and temperature (Refinetti and Menaker 1992), has a major input of serotonin-containing neurons originating in the raphe nuclei (Bosler and Beaudet 1985). In humans, agomelatine appears to possess positive phase-shifting properties. An advance in the sleep phase, a decline in body temperature, and a release of melatonin have been found following the administration of agomelatine (de Bodinat et al. 2010).

In a small case series, agomelatine at a dose of 50 mg/day was assessed in six patients, with and without other psychiatric comorbidities, who had been refractory to previous treatments with SRIs (Fornaro 2011). Three out of six patients showed a clinical improvement with a symptom reduction of at least 35 % as compared to the pre-treatment Y-BOCS scores which is regarded as a significant therapy response in current clinical trials (Pallanti et al. 2002). Another adult patient with clomipramine-refractory OCD who did not respond to augmentation with risperidone and aripiprazole was reported to show clinical improvement with agomelatine (da Rocha and Correa 2011). The ability of agomelatine to resynchronize circadian rhythms may demonstrate the important role of a disruption of these rhythms found in OCD. Since the regulation of the serotonergic system is circadian, a resynchronization of this system may affect serotonergic dysfunction known to be of importance in OCD (Wulff et al. 2010). Further investigations are needed to assess the efficacy of agomelatine as an augmentation strategy for therapy-refractory OCD.

Conclusion

The etiopathology and neurobiology of OCD are not fully understood. Hormonal dysregulation and a delayed sleep phase in patients with OCD point to a possible role of abnormal circadian rhythms in the pathophysiology of the disorder. The etiology of delayed sleep phase in individuals with OCD and its interaction with the core symptoms of OCD with regard to clinical function and disability remain to be investigated. In particular, prospective longitudinal assessments of sleep phase in OCD are needed. The contribution of comorbid depression is difficult to disentangle from that of OCD. Sleep disturbance is a core feature of major depression which is also the most common comorbid disorder of OCD (Weissman et al. 1994). It is therefore possible that DSPS occurring in OCD is related to comorbid depression. A number of concomitant clinical features that may be referable to bipolarity (Centorrino et al. 2006) may account for treatment refractoriness in some OCD cases. Future studies, therefore, should further elucidate the overlap between OCD and depression. The efficacy of agomelatine and the importance of a resynchronization of circadian rhythms in the therapy of OCD require further investigations. Adjunctive chronotherapy might also enhance the outcome in treatment-refractory OCD. In addition, the investigation of novel treatments such as light therapy or the administration of melatonin might be of interest.

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